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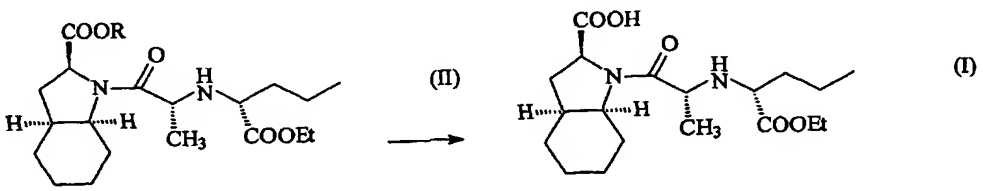
(54) Title: PERINDOPRIL



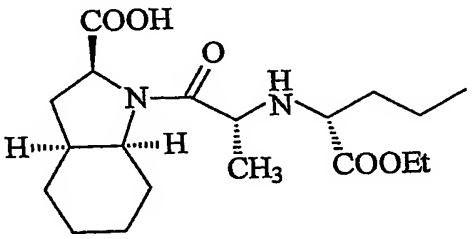
(57) Abstract: A pharmaceutically acceptable salt of perindopril of formula (I) is made from a protected precursor compound of formula (II) wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring so as to yield the corresponding free acid, which deprotection is carried out in the presence of a base which forms a pharmaceutically acceptable salt with said free acid formed by said deprotection.

PERINDOPRIL

This invention relates to a process for preparing a pharmaceutically acceptable salt of perindopril, and a novel polymorphic form thereof.

Perindopril is the international non-proprietary name of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}-octahydroindole-2-carboxylic acid. Perindopril is known to have therapeutic application as an angiotensin – converting enzyme (ACE) inhibitor. ACE is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to angiotensin II, as well as causing the degradation of bradykinin. Angiotensin II is a vasoconstrictor which also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE has, therefore, been shown to have therapeutic utility in patients suffering from disease states such as hypertension and congestive heart failure. In addition, it has been discovered that ACE inhibitors are useful in treating cognitive disorders.

Perindopril has the following structural formula (I)



(I)

Perindopril is described in US patent no. 4508729. Preparative processes described in this US patent are carried out in an alcoholic medium, and in the presence of a neutral dehydrating agent and an organic or inorganic cyanoborohydride. Deprotection processes can be carried out where necessary, for example with reference to hydrolysis and/or hydrogenolysis.

US patent no. 4914214 describes a process for the preparation of perindopril and its t-butylamine salt. The process comprises condensation of a protected ester of (2S,3aS,7aS)-2-carboxyperhydroindole with the (S,S) diastereoisomer of N-[(S)-1-carbethoxybutyl]-(S)-

alanine, followed by deprotection employing charcoal containing 5% palladium and water. Tertiary-butylamine is then added to yield the t-butylamine salt of perindopril.

PCT patent application WO 01/87835 describes a novel crystalline form, namely α crystalline form, of the t-butylamine salt of perindopril, processes of preparing the same and pharmaceutical formulations containing the same.

PCT patent application WO 01/87836 describes a novel crystalline form, namely Ǝ crystalline form, of the t-butylamine salt of perindopril, processes of preparing the same and pharmaceutical formulations containing the same.

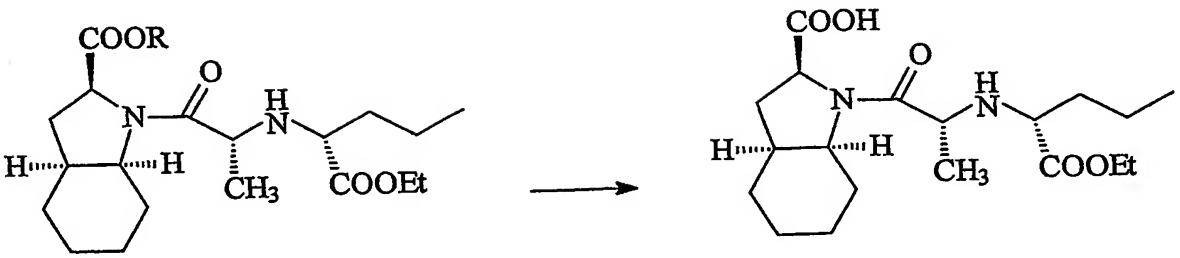
PCT patent application WO 01/87835 describes a novel crystalline form, namely γ crystalline form, of the t-butylamine salt of perindopril, processes of preparing the same and pharmaceutical formulations containing the same.

PCT patent application WO 01/58868 describes a process of preparing perindopril or pharmaceutically acceptable salts thereof, which process provides perindopril, or a salt thereof, with improved purity. More particularly, the level of known impurities associated with perindopril or a salt thereof, prepared according to PCT patent application WO 01/58868, is described as being less than 0.2 or 0.1% by weight. Intermediate process steps are carried out in the presence of 1-hydroxybenzotriazole, dicyclohexylcarbodiimide and optionally triethylamine, and at a temperature in the range of 20 to 77EC, followed by deprotection and where required salt conversion.

Prior art processes for the preparation of perindopril, or pharmaceutically acceptable salts thereof, have generally tended to be time-consuming and have often resulted in undesirable associated impurities, such as diketopiperazine analogues. There is, therefore, a need for an improved process for preparing perindopril, or pharmaceutically acceptable salts thereof, which alleviates the above mentioned problems.

We have now developed a process for preparing a pharmaceutically acceptable salt of perindopril, which is advantageous in terms of a faster reaction time compared to known processes for the preparation of a pharmaceutically acceptable salt of perindopril, and also in obviating the production of undesirable impurities so as to achieve a highly pure product.

In accordance with one aspect of the present invention, there is provided a process for preparing a pharmaceutically acceptable salt of perindopril of formula (I) from a protected precursor compound of formula (II)



(II) (I)

wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring so as to yield the corresponding free acid, which deprotection is carried out in the presence of a base which forms a pharmaceutically acceptable salt with said free acid formed by said deprotection.

Typically, R can represent any suitable carboxyl protecting group that can be selectively removed by a process according to the present invention. Preferably, R can represent optionally substituted aralkyl, especially optionally substituted benzyl. R can, therefore, typically represent unsubstituted benzyl; alternatively substituted benzyl can be employed, such as 4-halo substituted, or 4-C_{1-4}alkoxy substituted benzyl, especially 4-Cl benzyl, or 4-methoxy benzyl.

Suitably, deprotection as employed in a process according to the present invention can comprise hydrogenolysis in the presence of a noble metal catalyst, preferably palladium-on-chacoal.

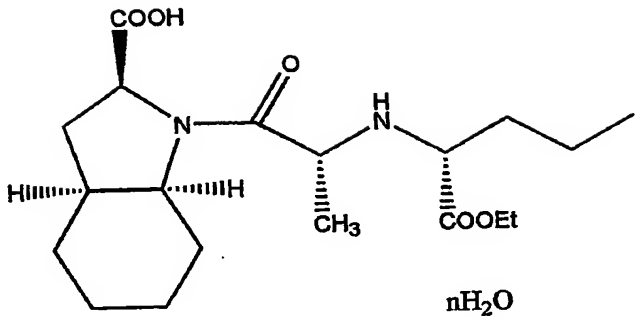
The process of the present invention is advantageous in achieving a highly pure product. A pharmaceutically acceptable salt of perindopril prepared by a process according to the present invention is preferably more than about 99% w/w pure, and more preferably more than about 99.5% w/w pure. The purity of a pharmaceutically acceptable salt of perindopril prepared by a process according to the present invention can be further enhanced by an optional crystallisation step in a suitable solvent, such as ethyl acetate, isopropanol or the like, so as to obtain a pharmaceutically acceptable salt of perindopril which is preferably about 99.8% w/w pure.

Preferably, the base employed in the process of the present invention is selected so as to form a pharmaceutically acceptable salt with the free acid formed by the deprotection as indicated above, whereby it is possible to obtain a pharmaceutically acceptable salt of perindopril directly from such a reaction work-up. In a particularly preferred embodiment according to the present invention the base comprises t-butylamine and as such a preferred process according to the present invention can provide a highly pure t-butylamine salt of perindopril directly from the reaction process.

According to the above preferred embodiment of the present invention, there is provided a process for preparing perindopril t-butylamine (which is well known to those of skill in the art as being perindopril erbumine) from a protected precursor compound of formula (II) substantially as hereinbefore described (preferably a benzyl protected precursor compound of formula (II) where R represents benzyl), which process comprises subjecting a compound of formula (II) to deprotection (preferably hydrogenolysis in the presence of a noble metal catalyst such as palladium-on-chacoal) of the carboxylic group COOR attached to the heterocyclic ring so as to yield the corresponding free acid, which deprotection is carried out in the presence of t-butylamine so as to form the t-butylamine salt of perindopril.

Suitably a precursor compound of formula (II) is initially dissolved in an alkanol solvent, such as isopropanol or the like, followed by addition of the base thereto. This is further followed by the deprotection of the carboxylic group COOR, suitably by the addition of palladium-on-charcoal and hydrogenation for several hours. The alkanol solvent is suitably concentrated under vacuum and replaced by a water immiscible solvent, such as ethyl acetate or the like. The resulting solids can then be cooled and filtered to yield a pharmaceutically acceptable salt of perindopril.

The process according to the present invention substantially as hereinbefore described may further comprises hydrating a pharmaceutically acceptable salt of perindopril obtained by the process so as to yield a pharmaceutically acceptable salt of hydrated perindopril of formula (Ia)



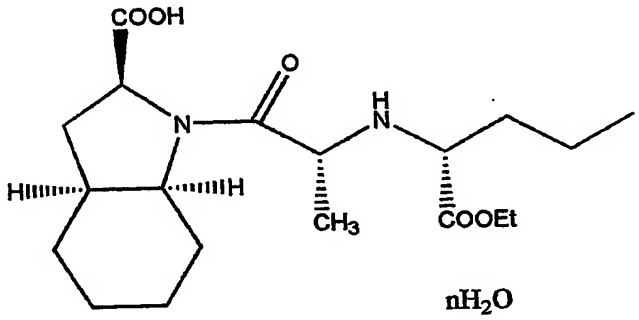
(Ia)

wherein n is an integer of 1 to 5, or a reciprocal of integers 2 to 5. Hydration can be by way of the addition of water or by drying in air.

Preferably n is 1, whereby a pharmaceutically acceptable salt of perindopril monohydrate is formed by a process according to the present invention.

The present invention also provides a process for preparing a monohydrate of a pharmaceutically acceptable salt of perindopril, which process comprises hydrating a pharmaceutically acceptable salt of perindopril so as to yield said monohydrate. Hydration can be by way of the addition of water or by drying in air, and preferably perindopril t-butylamine is hydrated to yield perindopril t-butylamine monohydrate.

The present invention further provides a pharmaceutically acceptable salt of perindopril optionally in hydrated form, prepared by a process substantially as hereinbefore described. In particular, a pharmaceutically acceptable salt of hydrated perindopril of formula (Ia) is provided



(Ia)

wherein n is an integer of 1 to 5, or a reciprocal of integers 2 to 5. Preferably, n is 1. A preferred pharmaceutically acceptable salt of hydrated perindopril of formula (Ia) is the t-butylamine salt. In a particularly preferred embodiment, the present invention provides perindopril t-butylamine (or erbumine) monohydrate.

The present invention also provides perindopril t-butylamine monohydrate having an X-ray diffractogram, or substantially the same X-ray diffractogram, as set out in Figure 1. More particularly, perindopril t-butylamine monohydrate according to the present invention can be characterised as having an X-ray powder diffraction pattern with characteristic peaks (2θ): 9.5504, 14.8600, 15.7486, 16.5400, 20.0400, 21.0499, 22.0600, 24.1744, 26.3300 and 27.1600.

Further characterising data for perindopril t-butylamine monohydrate according to the present invention as obtained by X-ray diffraction is shown in following Table 1.

Table 1

Peak No.	2θ (deg)	d (A)	I/II	FWHM (deg)	Intensity (Counts)	Integrated I (Counts)
1	8.6400	10.22611	10	0.57600	151	6899
2	9.5504	9.25324	73	0.50470	1090	28204
3	10.5940	8.34394	5	0.97200	79	4071
4	13.6000	6.50569	6	0.42860	91	2112
5	14.1400	6.25844	14	0.47120	215	5210
6	14.8600	5.95678	22	0.59000	332	10293
7	15.7486	5.62262	75	0.14270	1111	49244
8	16.5400	5.35533	30	0.72500	450	15749
9	17.5400	5.05220	16	0.67120	231	9128
10	18.6100	4.76406	17	0.56000	249	7981
11	20.0400	4.42722	31	0.51660	458	13471
12	21.0499	4.21704	100	0.90700	1488	63860
13	22.0600	4.02618	50	0.59480	747	23998
14	23.1600	3.83738	17	0.71720	253	12014

15	24.1744	3.67860	47	0.50030	705	17912
16	24.8000	3.58721	5	0.26000	73	1463
17	26.3300	3.38213	31	0.94000	468	19402
18	27.1600	3.28062	20	0.68500	292	9230
19	28.4444	3.13534	15	0.96890	223	11023
20	30.8000	2.90071	7	0.59340	99	3196
21	31.8000	2.81173	9	0.65600	130	4356
22	32.5600	2.74782	11	0.61340	163	4411
23	33.2400	2.69314	6	0.75000	95	3116
24	34.1800	2.62120	4	0.64000	61	2155
25	35.4728	2.52857	7	0.85430	104	4353
26	36.8838	2.43502	6	0.61900	93	2985
27	38.7340	2.32285	4	0.50800	55	1432

Perindopril as provided by the present invention has therapeutic utility as an ACE inhibitor.

In addition, the present invention further provides a method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of perindopril (preferably perindopril t-butylamine monohydrate) as provided according to the present invention.

The present invention also provides use of perindopril as provided according to the present invention (preferably perindopril t-butylamine monohydrate) in the manufacture of a medicament for inhibiting ACE.

A patient can be in need of treatment to inhibit ACE, for example when the patient is suffering from hypertension, chronic congestive heart failure, or the like. Inhibition of ACE reduces levels of angiotensin II and thus inhibits the vasopressor, hypertensive and hyperaldosteronemic effects caused thereby. Inhibition of ACE would also potentiate endogenous levels of bradykinin. An effective ACE inhibitory amount of perindopril as provided according to the present invention is that amount which is effective in inhibiting ACE in a patient in need thereof which results, for example, in a hypotensive effect.

In effecting treatment of a patient, perindopril as provided according to the present invention can be administered in any form or mode which makes the compound bioavailable

in effective amounts, including oral and parenteral routes. For example, perindopril as provided according to the present invention can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated and the stage of the disease.

Perindopril as provided according to the present invention can be administered in the form of pharmaceutical compositions or medicaments which are prepared by combining the perindopril according to the present invention with pharmaceutically acceptable carriers, diluents or excipients therefor, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

In another embodiment, the present invention provides pharmaceutical compositions comprising an effective ACE inhibitory amount of perindopril as provided according to the present invention (preferably perindopril t-butylamine monohydrate), together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient must be compatible with perindopril as provided according to the present invention, and not be deleterious to a recipient thereof.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier, diluent or excipient may be a solid, semi-solid, or liquid material, which can serve as a vehicle or medium for the active ingredient. Suitable carriers, diluents or excipients are well known in the art. Pharmaceutical compositions according to the present invention may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solutions, suspensions or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, a monohydrate according to the present invention may be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups and the like.

The tablets, pills, capsules, and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients,

such as starch or lactose; disintegrating agents such as alginic acid, corn starch and the like; lubricants, such as magnesium stearate; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration perindopril as provided according to the present invention may be incorporated into a solution or suspension. The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; and buffers such as acetates, citrates or phosphates. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The present invention will now be further illustrated by the following Figure and Examples, which do not limit the scope of the invention in any way.

Figure 1: X-ray diffraction pattern of perindopril erbumine monohydrate according to the present invention. The sample was analysed using a Shimadzu-6000 x-ray diffractometer. The source used was K_α monochromatic radiation of Cu having wavelength of 1.5406 A°. The Divergent Slit used was 1°. The Receiving Slit was 0.30mm. The Scintillation counter was used as the detector, with the range being from 3° to 40° (2θ) with a scan speed of 2° per minute.

Example 1

The benzyl ester of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}-octahydroindole-2-carboxylic acid, namely benzyl perindopril, (10gms) was dissolved in isopropanol (100ml). To the clear solution, t-butylamine (2.5gms) and 10% w/w

palladium on charcoal (2gms) was added. The reaction mixture was hydrogenated at a pressure of 1kg/cm^2 for 2 hours.

The reaction mass was filtered to remove the catalyst. The solvent was concentrated under vacuum and isopropanol was replaced by simultaneous addition of ethyl acetate. The solids obtained were cooled to 0EC and filtered to obtain perindopril erbumine (7.8gms).

Example 2

Perindopril erbumine (10gms) was suspended in acetone (80ml). To this was added water (0.4ml) and the contents heated to dissolve the solids and cooled to ambient. The resulting slurry was filtered to obtain perindopril erbumine monohydrate (9.4gms).

Example 3

Perindopril erbumine (20gms) was suspended in ethyl acetate (300ml). To this was added water (1.5ml) and the contents heated to dissolve the solids and cooled to 10EC. The resulting slurry was filtered to obtain perindopril erbumine monohydrate (17gms).

Example 4

Perindopril erbumine (5gms) was suspended in acetonitrile (75ml). To this was added water (0.4ml) and the contents heated to dissolve the solids and cooled to 0EC. The resulting slurry was filtered to obtain perindopril erbumine monohydrate (2.9gms).

Example 5

Perindopril erbumine (20gms) was suspended in ethyl acetate (300ml). The contents were heated to dissolve the solids and cooled to 10EC. The resulting slurry was filtered and dried in air having a relative humidity of at least 75% to give perindopril erbumine monohydrate (17gms).

Example 6

Preparation of perindopril erbumine monohydrate

Raw Materials :-

1. Perindopril erbumine anhydrous = 10 gm.
2. Isopropyl alcohol = 70 ml.

3. Water = 2 ml.
4. Ethyl acetate = 85 ml.

Procedure :-

1. Charge 10 gm of perindopril erbumine (anhydrous) in round bottom flask. Add 70 ml isopropyl alcohol. Stir for ½ hr. (around 95% product dissolved).
2. Add 2 ml of water. Stir for 15 min (clear solution obtained).
3. Stir reaction mass at 38-40°C for 2 hrs.
4. Distill out isopropyl alcohol completely under vacuum (below 600 mm) below 40°C. (Gel type material observed.)
5. Charge 30 ml ethyl acetate. Stir for 15 min below 40°C (clear solution observed). Distill under vacuum below 40°C (semi-solid observed).
6. Charge 40 ml ethyl acetate at 36-38°C. Stir for 15 min (free solid observed).
7. Stir 1 hr at room temperature (25-30°C). (Free crystalline solid observed.)
8. Cool to 10°C. Stir for 2 hrs.
9. Filter solid and wash with 15 ml ethyl acetate. Suck dry for 2 hrs.
10. Dry under vacuum below 40°C for 12 hrs.

Water Content =3.2-3.8%

M.P = 145-150°C.

Example 7

The following tablets were prepared:

(a) Formulation I:

	Strengths		
	2 mg	**4 mg**	**8 mg**
Ingredients			
Perindopril Erbumine Monohydrate	2 mg	4 mg	8 mg
Maize starch	5 mg	10 mg	20 mg
Lactose anhydrous	12.5 mg	25.0 mg	100.0 mg
Microcrystalline cellulose	25.10 mg	50.20 mg	100.40 mg

Magnesium stearate	0.4	0.8	1.6
Total weight	45.0 mg	90.0 mg	180.0 mg

Procedure: Sift the above ingredients through respective sieves. Mix the ingredients in a suitable blender. Compress the tablets in the suitable toolings.

(b) Formulation II:

	Strengths		
	2 mg	**4 mg**	**8 mg**
Ingredients			
Perindopril Erbumine Monohydrate	2 mg	4 mg	8 mg
Maize starch	10 mg	10 mg	10 mg
Lactose anhydrous	25 mg	25.0 mg	25.0 mg
Microcrystalline cellulose	52.2 mg	49.20 mg	45.20 mg
Yellow oxide of Iron	-	1.0	-
Red oxide of Iron	-	-	1.0
Hydrogenated castor oil	0.8 mg	0.8 mg	0.8 mg
Total weight	90.0 mg	90.0 mg	90.0 mg

Procedure:

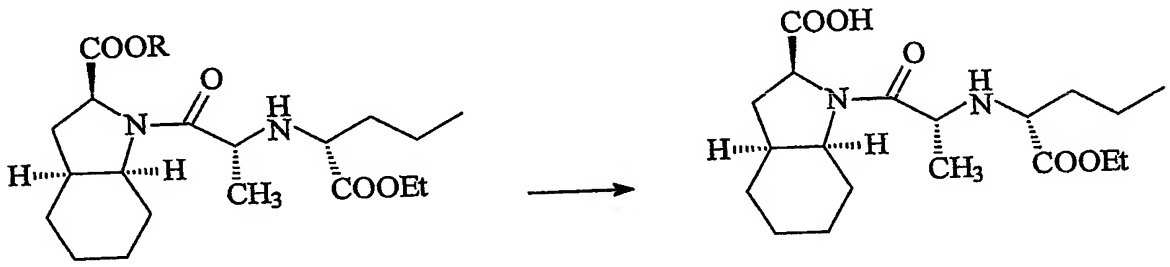
1) Dissolve Perindopril Erbumine Monohydrate in ethanol.

2) Granulate the above ingredients except hydrogenated castor oil with the above solution. Dry the granules and size.

3) Lubricate with hydrogenated castor oil in suitable blender. Compress the granules in the suitable tooling

CLAIMS

1 A process for preparing a pharmaceutically acceptable salt of perindopril of formula (I) from a protected precursor compound of formula (II)



(II) (I)

wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring so as to yield the corresponding free acid, which deprotection is carried out in the presence of a base which forms a pharmaceutically acceptable salt with said free acid formed by said deprotection.

2 A process according to claim 1, wherein R represents optionally substituted aralkyl.

3 A process according to claim 2, wherein R represents unsubstituted benzyl.

4 A process according to claim 2, wherein R represents 4-halo substituted, or 4-C_{1-4}alkoxy substituted benzyl.

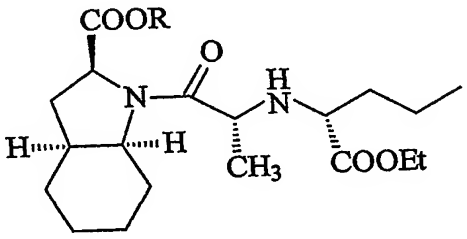
5 A process according to claim 4, wherein R represents 4-Cl benzyl, or 4-methoxy benzyl.

6 A process according to any of claims 1 to 5, wherein deprotection comprises hydrogenolysis in the presence of a noble metal catalyst.

7 A process according to claim 6, wherein the noble metal catalyst comprises palladium-on-chacoal.

8 A process according to any of claims 1 to 7, wherein said base comprises t-butylamine.

9 A process for preparing perindopril t-butylamine from a protected precursor compound of formula (II)



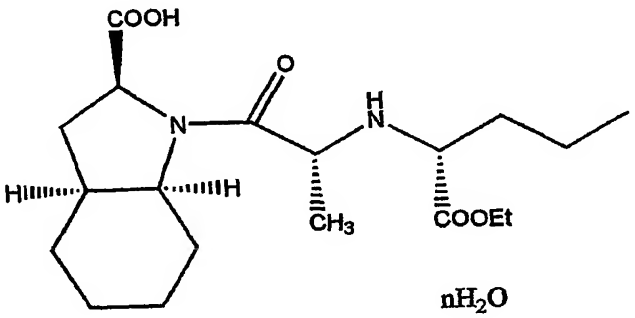
(II)

wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring so as to yield the corresponding free acid, which deprotection is carried out in the presence of t-butylamine so as to form the t-butylamine salt of perindopril.

10 A process according to claim 9, wherein R represents unsubstituted benzyl.

11 A process according to claim 9 or 10, wherein deprotection comprises hydrogenolysis in the presence of palladium-on-chacoal.

12 A process according to any of claims 1 to 11, which further comprises hydrating a pharmaceutically acceptable salt of perindopril obtained by said process so as to yield a pharmaceutically acceptable salt of hydrated perindopril of formula (Ia)



(Ia)

wherein n is an integer of 1 to 5, or a reciprocal of integers 2 to 5.

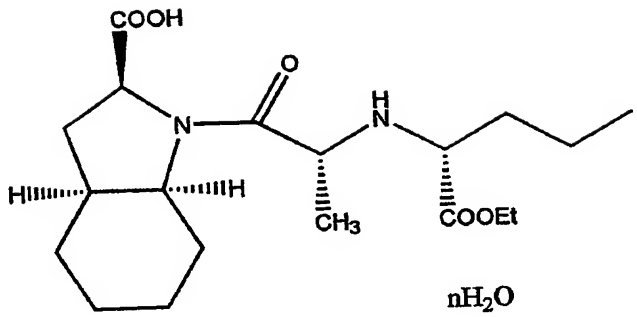
13 A process according to claim 12, wherein n is 1.

14 A process for preparing a monohydrate of a pharmaceutically acceptable salt of perindopril, which process comprises hydrating a pharmaceutically acceptable salt of perindopril so as to yield said monohydrate.

15 A process according to any of claims 12 to 14, wherein perindopril t-butylamine is hydrated to yield perindopril t-butylamine monohydrate.

16 A pharmaceutically acceptable salt of perindopril optionally in hydrated form, prepared by a process according to any of claims 1 to 15.

17 A pharmaceutically acceptable salt of hydrated perindopril of formula (Ia)



(Ia)

wherein n is an integer of 1 to 5, or a reciprocal of integers 2 to 5.

18 A pharmaceutically acceptable salt according to claim 17, where n is 1.

19 A pharmaceutically acceptable salt according to claim 17 or 18, which is the t-butylamine salt.

20 Perindopril t-butylamine monohydrate.

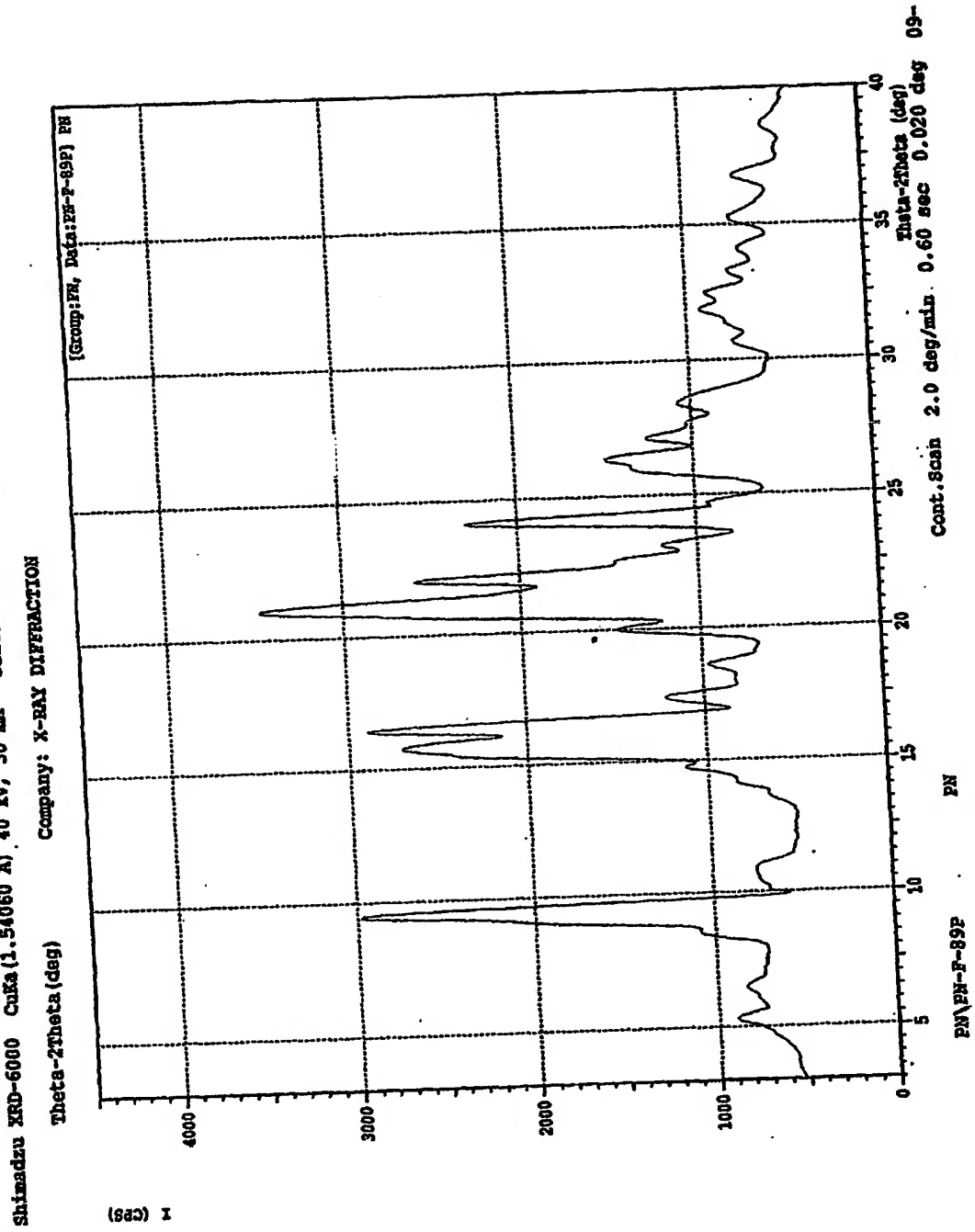
21 Perindopril t-butylamine monohydrate having an X-ray diffractogram, or substantially the same X-ray diffractogram, as set out in Figure 1.

22 Perindopril t-butylamine monohydrate characterised as having an X-ray powder diffraction pattern with characteristic peaks (2θ): 9.5504, 14.8600, 15.7486, 16.5400, 20.0400, 21.0499, 22.0600, 24.1744, 26.3300 and 27.1600.

23 A pharmaceutical composition comprising an effective ACE inhibitory amount of a pharmaceutically acceptable salt of perindopril according to any of claims 16 to 22, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

24 Use of a pharmaceutically acceptable salt of perindopril according to any of claims 16 to 22, in the manufacture of a medicament for inhibiting ACE.

25 A method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of a pharmaceutically acceptable salt of perindopril according to any of claims 16 to 22.


Shimadzu XRD-6000 CuKa(1.54060 A) 40 kV, 30 mA Slits: DS:1.00 deg, SS:1.00 deg, RS:0.30 mm
Company: X-RAY DIFFRACTION
Theta-2Theta(deg)
I (cps)
[Group:PN, Data:PN-F-89P] PN
Cont.Scan 2.0 deg/min 0.60 sec 0.020 deg
Theta-2Theta (deg)
PN\PN-F-89P
PN

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/04981

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/062 A61K38/05 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 914 214 A (BALIARDA JEAN ET AL) 3 April 1990 (1990-04-03) cited in the application	14-25
Y	column 6; claims 1-5; example 3D	1-13
X	VINCENT M ET AL: "Stereoselective Synthesis of a New Perhydroindole Derivative of Chiral Iminodiacid, a Potent Inhibitor of Agiotensin Converting Enzyme" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 23, no. 16, 1982, pages 1677-1680, XP002155080 ISSN: 0040-4020	14-25
Y	the whole document	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2004	17/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmidt, Harald

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/04981

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VINCENT M ET AL: "SYNTHESIS AND ACE INHIBITORY ACTIVITY OF THE STEREOISOMERS OF PERINDOPRIL (S 9490) AND PERINDOPRILATE (S 9780)" DRUG DESIGN AND DISCOVERY, HARWOOD ACADEMIC PUBLISHERS GMBH, XX, vol. 9, no. 1, 1992, pages 11-28, XP000885876 ISSN: 1055-9612	14-25
Y	page 18	1-13
X	EP 0 049 658 A (ADIR) 14 April 1982 (1982-04-14)	14-25
Y	page 12, line 31 -page 13, line 12; claims 1-11; example 2; table 1	1-13
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 22, 9 March 2001 (2001-03-09) & JP 2001 122780 A (DAI ICHI SEIYAKU CO LTD), 8 May 2001 (2001-05-08) abstract	
A	WO 01 83439 A (GINOT YVES MICHEL ;ADIR (FR); COQUEREL GERARD (FR); PFEIFFER BRUNO) 8 November 2001 (2001-11-08) the whole document	

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/GB 03/04981

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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PCT/GB 03/04981

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Information on patent family members

Application No
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